Annals of Clinical and Analytical Medicine
Original Research

Trimethylamine N-Oxide levels increase in patients with severe and non-severe COVID-19

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Abstract

Aim: This study aimed to measure and evaluate serum trimethylamine N-oxide (TMAO) levels in patients with COVID-19.

Material and Methods: The patients were divided into three groups according to their polymerase chain reaction (PCR) results and the clinical picture of the disease: Group 1 (negative PCR result, n = 44), Group 2 (positive PCR result and non-severe disease, n = 38) and Group 3 (positive PCR result and severe disease, n = 45).

Results: TMAO levels were significantly different among the three patient groups. Post Hoc Dunn's analysis revealed a significant difference between Group 1 and Group 2 ($p = 0.006$), Group 1 and Group 3 ($p < 0.001$) and Group 2 and Group 3 ($p = 0.031$). ROC analysis revealed that a cut-off value of 2.92 had a sensitivity of 74.70%, a specificity of 68.18%, a positive predictive value of 81.6% and a negative predictive value of 58.8%.

Discussion: The results of this study demonstrated that TMAO levels increased in the patients with COVID-19, and further TMAO levels increased as the severity of the disease progressed.

Keywords

Biomarkers, COVID-19, Peripheral Blood, Severe, Trimethylamine N-oxide

DOI: 10.4328/ACAM.21403 Received: 2022-09-21 Accepted: 2022-10-28 Published Online: 2022-11-15 Printed: 2023-01-01 Ann Clin Anal Med 2023;14(1):30-34
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This study was approved by the Ethics Committee of Harran University (Date: 2021-03-01, No: HRU/21.05.31)

Introduction

In December 2019, an outbreak of viral pneumonia was reported in Wuhan, Hubei Province, China, and the cause of this outbreak was identified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). As the disease rapidly spread worldwide, the World Health Organization (WHO) renamed it coronavirus disease 2019 (COVID-19) in February 2020 [1].

The SARS-CoV-2 virus causes respiratory problems along with shock, acute kidney damage and vascular and thromboembolic complications. In addition, previous studies have reported that endothelial cell infection leads to conditions such as vascular thrombosis, pulmonary edema and the deterioration of pulmonary perfusion in patients with COVID-19. SARS-CoV-2 binds to the angiotensin-converting enzyme 2 (ACE2) protein, entering the host target cells and stimulating interleukin (IL) synthesis and inflammatory activation following interaction with toll-like receptors, further triggering a cascade of responses [2]. In addition to the risk factors of advanced age and underlying chronic diseases (cardiovascular diseases (CVDs), diabetes mellitus (DM), respiratory diseases), several factors that affect the course of COVID-19 have been defined [3].

Diet is a major factor that affects the prevalence of numerous diseases. Intestinal dysbiosis can contribute to the abnormal inflammatory response triggered by SARS-CoV-2 [4]. Trimethylamine N-oxide (TMAO), an oxygenated product of trimethylamine (TMA) generated by intestinal microbiota, is an amine oxide found in our body [5]. Several types of bacteria, including Clostridia, Proteus, Shigella and Aerobacter, are involved in TMA production [6]. TMAO is a naturally occurring osmolyte that protects the intracellular components from destructive stress conditions [7]. In particular, previous studies have shown that TMAO can improve protein stability and prevent the denaturing effect of urea [8]. Both observational and experimental studies have demonstrated the ability of TMAO to cause inflammatory endothelial damage [9,10]. Recent studies have further revealed that TMAO induces pro-inflammatory cytokine release and increases inflammatory response [11]. There have also been studies reporting that TMAO is associated with chronic heart failure, atherosclerosis, peripheral venous disease, pneumonia, chronic kidney disease, colorectal cancer, obesity and Parkinson's disease [12-14]. Nutritional strategies such as limiting the high intake of choline and carnitine, which are the precursors of TMAO, are viable options for COVID-19 management; however, these molecules are essential for the maintenance of body health. Therefore, the aim of the present study was to determine the serum TMAO levels according to the clinical course of COVID-19 in the patients who were diagnosed with it.

Material and Methods

Ethical approval for this study was obtained from the local ethics committee. The patients who presented to the emergency department with the suspicion of COVID-19 were included in the study. The sample size was calculated using the G*Power version 3.1.9.2 (Germany) software. With a power of 80%, 0.05 level of statistical significance and effect size of 0.6, the sample size for each group was calculated to be 30. The basic characteristics, symptoms the patients presented with at the time of admission to the emergency department and laboratory test results of the patients were recorded in the prepared data form. The patients were divided into three groups according to their polymerase chain reaction (PCR) results and the clinical picture of the disease: Group 1 (negative PCR result, n = 44), Group 2 (positive PCR result with non-severe disease, n = 38) and Group 3 (positive PCR result with severe disease, n = 45). The severity of COVID-19 was defined according to the 2020 WHO Guideline. Severe COVID-19 was defined by any of the following: oxygen saturation <90% in room air, severe respiratory distress symptoms (accessory muscle use, inability to complete full sentences, and severe chest wall indrawing, grunting, central cyanosis in children or the presence of any other general danger signs). Non-severe COVID-19 was defined as the absence of the abovementioned signs of severe or critical COVID-19 [15].

Biochemical analysis

Blood samples were taken from all the patients on admission. The samples were then centrifuged for 10 min at 3000 rpm, and the serum was stored at −80°C in aliquots till the day of analysis. The TMAO levels were measured using enzyme-linked immunosorbent assays (Catalogue No: 201-127378, Shanghai Sunred Biological Technology Co., Ltd., Shanghai, China) according to the manufacturer's instructions.

The white blood cell (WBC, normal range [NR]: 3.7–10.1 10e3/uL,), hemoglobin (HGB, NR: 12–18.1 g/dL,), hematocrit (HCT, NR: 35–53.7%) and platelet (PLT, NR: 140–360 10e3/uL) levels were determined using Alinity HQ (Abbott, USA).

The serum blood urea nitrogen (BUN, NR: 19–50 mg/d), creatinine (NR: 0.55–1.02 mg/dL), alanine aminotransferase (ALT, NR: 7–40 U/L), aspartate aminotransferase (AST, NR: 13–40 U/L), lactate dehydrogenase (LDH, NR: 120–246 U/L), C-reactive protein (CRP, NR: 0–0.5 mg/dL), bilirubin (NR: 0,3–1,2 mg/dL) and ferritin (NR: ferritin: 22–322 ng/mL) levels were measured by conventional laboratory methods on Atellica Solution (Siemens Healthineers, Germany).

The tests for plasma fibrinogen levels (NR: 160–450 mg/dL), D-dimer levels (NR: 0–0.55 mg/L), prothrombin time (PTT) (NR: 10.5–15.5 sec), activated partial thromboplastin time (aPTT, NR: 22–36 sec) and International Normalized Ratio (INR, NR: 0.8–1.2) were conducted using the Sysmex CS2100i device (Sysmex, Japan).

Statistics

Statistical analysis was performed using the SPSS 21.0 (IBM Corporation, Armonk, NY, USA) and MedCalc (Version 10.1.6.0, Ostend, Belgium) packages. Numerical data were expressed as mean ± standard deviation. Qualitative data were expressed as numbers and percentages. The Shapiro–Wilk test was used to assess whether the data conformed to a normal distribution. The Kruskal–Wallis test was used to compare the variables between the three groups. Following the Kruskal–Wallis test, binary comparisons were made using the Post Hoc Dunn's test. For the comparison of categorical data, Pearson's Chi-square test was used if the percentages of less than five theoretical frequencies were less than 20% and Fisher's exact test was used otherwise. Following the Chi-square test, binary comparisons were made using the Post Hoc Z test. Spearman's correlation analysis was performed to determine the relationship between the TMAO

levels and other continuous variables. Receiver operating characteristic (ROC) curve analysis was performed to determine whether the TMAO levels could be used to distinguish between the patients with PCR positive and negative results. The ROC curve analysis results were presented as % specificity, % sensitivity (area under the ROC curve [AUC], p, 95% confidence interval [CI]). $p < 0.05$ was accepted as statistically significant in all analyses.

Ethical Approval

Ethics Committee approval for the study was obtained.

Results

Of the 127 patients included in our study, 44 were in Group 1 (F/M = 13/31), 38 in Group 2 (F/M = 17/21) and 45 in Group 3 (F/M = 22/23). No difference was found among the groups regarding sex (p = 0.147), but the mean age was significantly different among the three groups (p < 0.001). The patients presented to the emergency department with fever, cough, shortness of breath, sore throat, runny nose, fatigue, muscle–joint pain, headache, loss of taste and smell and diarrhoea. The most frequent symptoms in Group 1 were shortness of breath and muscle–joint pain, in Group 2, the most frequent symptoms were fatigue and cough and in Group 3, the most frequent symptoms were cough and shortness of breath. The frequency

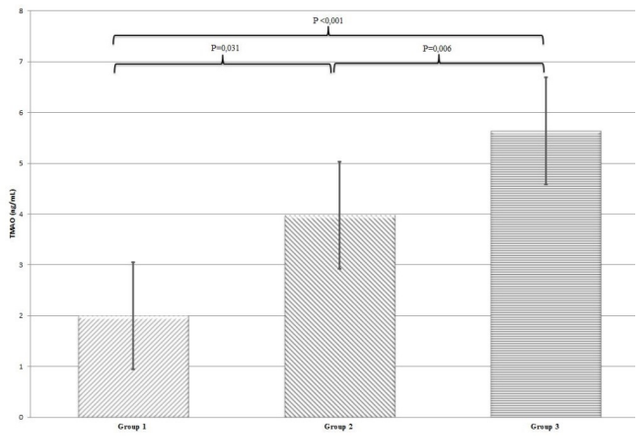

Figure 1. Comparison of the trimethylamine N-oxide levels among the groups

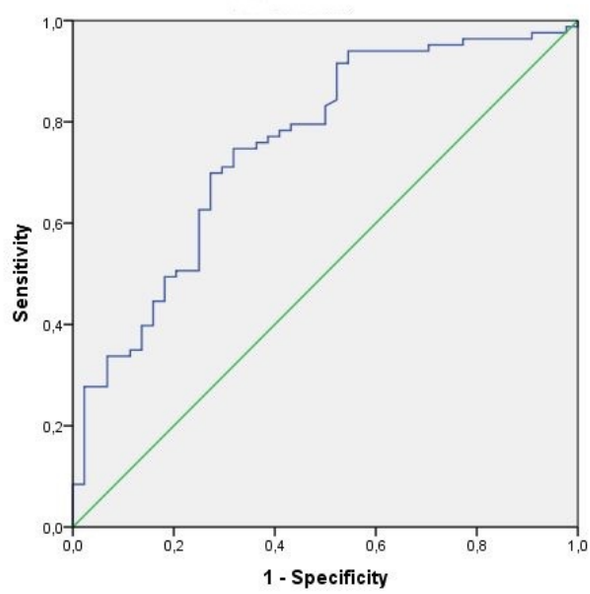

Figure 2. Receiver operating characteristic analysis for the use of the trimethylamine N-oxide levels to distinguish between the patients with and without Covid-19

Table 1. Comparison of patient characteristics

	PCR negative	PCR positive Non-severe	PCR positive Severe	p
N (F/Total)	13/44	17/38	22/45	0.147
Age	54.5 (34–75)[a]	44 (20–72)[b]	65 (38–95)[c]	<0.001*
Fever n (%)	14 (%31.8)[d]	11 (%28.9)[d]	23 (%51.1)[d]	0.071¶
Cough n (%)	18 (40.9%)[d]	27 (71.1%)[e]	35 (77.8%)[e]	0.001¶
Shortness of breath n (%)	22 (50%)[d]	19 (50%)[d]	43 (95.6%)[e]	0.001¶
Sore throat n (%)	14 (31.8%)[d]	21 (55.3%)[e]	14 (31.1%)[d]	0.041¶
Runny nose n (%)	10 (22.7%)[d]	7 (18.4%)[d]	2 (%2.4)[e]	0.042¶
Fatigue n (%)	11 (25%)[d]	30 (%78.9)[e]	43 (%88)[e]	<0.001¶
Muscle–joint pain n (%)	22 (%50)[d]	21 (%55.3)[d]	22 (%48.9)[d]	0.830¶
Headache n (%)	19 (43.2%)[d]	16 (42.1%)[d]	17 (20.5%)[d]	0.861¶
Loss of taste and smell n (%)	12 (27.3%)[d]	10 (26.3%)[d]	15 (33.3%)[d]	0.739¶
Diarrhea n (%)	16 (36.4%)[d]	7 (18.4%)[d]	11 (24.4%)[d]	0.170¶
HT	18 (40.9%)[d]	5 (13.2%)[e]	16 (35.6%)[d]	0.017¶
DM	4 (9.1%)[d]	3 (7.9%)[d]	14 (31.1%)[e]	0.005¶
CVD	12 (27.3%)[d]	3 (7.9%)[e]	13 (28.9%)[d]	0.026¶
COPD	5 (11.4%)[d]	5 (13.2%)[d]	5 (11.1%)[d]	0.953¶

*Kruskal–Wallis test; [a, b and c]: indicate no statistically significant difference between the groups with the same letter according to the Post Hoc Dunn's test. ¶ Chi-square test; [d and e]: indicate no statistically significant differences between groups with the same letter according to the Post Hoc Z-test after the Chi-square test. PCR: polymerase chain reaction; HT: hypertension; DM: diabetes mellitus; CVD: cardiovascular diseases; COPD: chronic obstructive pulmonary disease

Table 2. Comparison of basic laboratory findings between patient groups

	PCR positive			p*
	PCR negative	Non-severe	Severe	
WBC (10e3/uL)	6.1 (4.9–15.2)[a]	5.7 (3.1–19)[a]	9 (2.3–21)[b]	0.001
Hgb (g/dL)	13 (10–17)[a]	13.5 (8–16)[a]	14 (10–16)[a]	0.782
HCT (%)	42 (33–53)[a]	44 (27–52)[a]	43 (30–50)[a]	0.816
Thrombocyte (10e3/uL)	207 (115–381)[a]	237 (120–510)[a]	205 (113–510)[a]	0.554
PTT (sec)	11.4 (10.1–19.9)[a]	11 (10–15)[a]	11 (10–13)[a]	0.674
INR	0.93 (0.81–1.62)[a]	0.80 (0.7–1.2)[a]	0.90 (0.80–1.10)[a]	0.560
aPTT (sec)	24 (17.3–29.6)[a]	23 (19–44)[a]	25 (17.4–39)[a]	0.488
D-dimer (mg/dL)	0.23 (0.05–8.12)[a]	0.30 (0.10–4.00)[a]	0.50 (0.10–7.50)[b]	0.001
Fibrinogen (mg/dL)	424 (181–715)[a]	367 (197–816)[a]	457 (287–850)[b]	0.008
Ferritin (ng/mL)	146 (24–573)[a]	147(14–1276)[a]	625 (20–2728)[b]	<0.001
LDH (U/L)	277 (160–1723)[a, b]	241 (123–807)[a]	343 (149–588)[b]	0.015
CRP (mg/dL)	2.05 (0.05–15)[a]	7.5 (0.30–42)[b]	16.7 (0.53–192)[c]	<0.001
ALT (U/L)	29.5 (10–151)[a]	27.5 (12–139)[a]	31 (13–309)[a]	0.971
AST (U/L)	30 (15–176)[a]	48 (19–84)[a]	44 (18–199)[a]	0.169
Bilurubin (mg/dL)	0.55 (0.10–2.70)[a]	0.60 (0.20–1.20)[a]	0.60 (0.20–3.10)[a]	0.485
Urea (mg/dL)	33 (11–55)[a]	27 (5–59)[b]	40 (19–136)[c]	<0.001
Creatine (mg/dL)	0.80 (0.56–1.48)[a]	0.83 (0.40–1.20)[a]	1.00 (0.70–3.00)[b]	<0.001
TMAO (ng/mL)	2 (0.18–11)[a]	3.98 (0.14–12.14)[b]	5.64 (0.84–13.72)[c]	<0.001

*Kruskal–Wallis test; [a, b and c]: indicate no statistically significant difference between the groups with the same letter according to the Post Hoc Dunn's test. PCR: polymerase chain reaction; WBC: white blood cell; Hgb: hemoglobin; HCT: hematocrit; PTT: prothrombin time; INR: International Normalized Ratio; aPTT: activated partial thromboplastin time; LDH: lactose dehydrogenase; CRP: C-reactive protein; ALT: alanine aminotransferase; AST: aspartate aminotransferase; TMAO: trimethylamine N-oxide

of cough, shortness of breath and fatigue was significantly higher in Group 3 than in the other groups. Symptoms of the patients at admission and their accompanying comorbidities are presented in Table 1.

Although a significant difference in the WBC, prothrombin time (PT) and INR values between the patient groups was observed, all the values were within normal clinical ranges. The D-dimer, ferritin, CRP, urea and creatinine values were significantly higher in the patients with severe COVID-19. The basic hemogram and biochemical examination results of the patients are given in Table 2.

The Kruskal–Wallis test results showed that the TMAO levels were significantly different among the three patient groups. Dunn's Post Hoc analysis revealed a significant difference between Group 1 and Group 2 ($p = 0.006$), Group 1 and Group 3 ($p < 0.001$) and Group 2 and Group 3 ($p = 0.031$) (Figure 1).

ROC analysis was performed to determine the TMAO concentration that can be used to distinguish PCR positive (Groups 2 and 3) and negative patients (Group 1). ROC analysis revealed that a cut-off value of >2.92 ng/mL had a sensitivity of 74.70%, specificity of 68.18%, a positive predictive value of 81.6% and a negative predictive value of 58.8%. (AUC = 0.753, 95% CI: 0.669–0.825, $p < 0.001$) (Figure 2).

No significant correlation was found between the TMAO levels and the levels of D-dimer ($r = -0.004$, $p = 0.970$), CRP ($r = 0.161$, $p = 0.147$) and WBC ($r = 0.042$, $p = 0.705$) in the patients with positive PCR results for COVID-19.

Discussion

The results of the present study showed that the TMAO levels were significantly increased in the patients with COVID-19 and the severity of the infection exacerbated this effect. The gastrointestinal tract is home to a complex, highly diverse microbial ecosystem that interacts with the host and ensures the establishment and permanence of immune homeostasis. It is known that dysbiosis and intestinal microbial metabolites act on systemic immunity, contributing to or protecting against the development of inflammatory events and diseases. Intestinal microbial metabolites affect the immune response of the lungs [16]. There have been limited studies on the underlying mechanism of TMAO level change in lung diseases. Ottiger et al. evaluated 317 patients with community-acquired pneumonia and found that the TMAO levels increased significantly in the non-surviving patients than in the surviving patients. They further reported that the TMAO levels were associated with long-term fatal outcomes in patients with pneumonia without prominent coronary artery disease [17]. Although the pathology of COVID-19 primarily involves the lungs, its complications increase in the presence of systemic diseases. It has been reported that the effects of COVID-19 are more adverse in those with impaired immune responses and comorbidities, such as obesity, atherosclerosis, type 2 DM and hypertension (HT) [18]. In the present study, a significant difference was found in the occurrence of HT, DM and CVD between the patients with severe and non-severe COVID-19. Furthermore, the comorbidity rate was higher in the patients with severe COVID-19. However, although the TMAO levels were significantly different between the patients without COVID-19 and with severe COVID-19, no difference was found in the comorbidities HT, chronic obstructive pulmonary disease and CVD except for DM. Hence, only DM among the comorbidities can have a potential effect on the TMAO levels in the patients with severe COVID-19. In addition, high TMAO levels are associated with abnormal inflammation that is exacerbated by SARS-CoV-2 infection [4]. Therefore, besides comorbidities, the increased levels of TMAO may be due to the close relationship of the disease with inflammatory processes.

Intestinal microbial metabolites can affect other organs besides the lungs. Although its advantages and disadvantages in the human body remain controversial and its underlying molecular mechanisms remain unclear, studies have shown that TMAO, a microbial metabolite, is linked to cardiovascular and metabolic diseases. Previous studies have reported the ability of TMAO to cross the blood-brain barrier, and in vitro studies have revealed that it supports cellular α-synuclein clustering, neuroinflammation, mitochondrial dysfunction and neuronal aging [19]. In the study by Sankowski et al [20], increased TMAO levels were observed in the cerebrospinal fluid and plasma of the patients with Parkinson's disease. Kuhn et al [21] investigated the relationship of TMAO, which plays a role in inflammation and neuroinflammation, with another inflammatory indicator, CRP, and reported no increase in the high-sensitivity CRP levels despite an increase in the TMAO plasma concentration. Furthermore, Ottiger et al found that although the baseline CRP levels were higher in patients with community-acquired pneumonia, TMAO levels were significantly increased in patients who died [17]. In the present study, however, it was determined that the CRP level was significantly increased in patients with severe COVID-19, but there was no significant correlation between the TMAO and CRP levels in the patients with COVID-19.

TMAO is known to increase the risk of atherothrombosis, and Zhu et al [22] showed that intestinal microorganisms directly contributed to platelet hyper-reactivity and increased thrombosis potential through the production of TMAO. The authors also found that TMAO-administered mice displayed significantly increased cell permeability and neo-intimal formation associated with increased IL-1β production in the intima. IL-1β is a powerful tissue factor inducer and also an indirect indicator of increased atherothrombosis risk caused by the increased levels of TMAO. Similarly, fibrinolysis has been associated with poor prognosis in patients with COVID-19. For these reasons, increased D-dimer levels are associated with poor prognosis in COVID-19 due to the extensive production of thrombins and the suspicion of fibrinolysis, which led the authors to assume that increased D-dimer concentrations were indicative of the existence of venous thromboembolisms, which can lead to ventilation–perfusion incompatibility [23]. Zang et al [24] evaluated 343 patients with COVID-19 and found that the mortality rate was higher in the patients with D-dimer levels of ≥2.0 µg/mL compared with the patients with D-dimer levels of <2.0 µg/mL. Similar to this result, in another study, ≥1.0 µg/mL D-dimer levels at the time of admission were associated with higher intra-hospital mortality in patients with COVID-19 [3]. In the present study, despite significant differences in the initial TMAO levels among the patient groups, no significant

difference was found between the patients with severe and non-severe COVID-19 despite the initially higher D-dimer levels in the patients with severe COVID-19. No significant difference was found in the initial D-dimer levels between the surviving and non-surviving patients. Furthermore, no correlation was found between the TMAO and D-dimer levels.

The results of this study showed that the levels of TMAO, a pro-inflammatory substance produced by intestinal microbiota, which is a part of the immune system, were increased in the patients with COVID-19, and the TMAO levels further increased as the severity of the disease progressed.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

Funding: *None.*

Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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How to cite this article:

İbrahim Halil Yasak, Mustafa Yılmaz, Mehmet Resat Ceylan, İsmail Koyuncu, Eyyup Sabri Seyhanlı. Trimethylamine N-Oxide levels increase in patients with severe and non-severe COVID-19. Ann Clin Anal Med 2023;14(1):30-34

This study was approved by the Ethics Committee of Harran University (Date: 2021-03-01, No: HRU/21.05.31)